5. Executive Summary - Clinical Studies and Information

Presented herein is clinical information to support use of the PMA devices. The primary study to support safety and effectiveness is the pivotal SAPPHIRE Study. Additional clinical studies and information that may be relevant are also provided.

SAPPHIRE Pivotal Clinical Study

The Cordis SAPPHIRE clinical study was conducted as the pivotal study to support the PMA application. Results demonstrate safety and effectiveness of the study devices in treatment of carotid artery disease in patients who are at high risk for surgery.

Background: SAPPHIRE was designed as a multi-center, prospective, randomized trial comparing carotid stenting with distal protection to carotid endarterectomy (CEA) in high-risk patients. The study design also included separate stent and CEA non-randomized (or registry) arms. Patients who met all entry criteria, but were determined by the surgeon to be too high-risk for CEA, and therefore unable to be randomized, were entered into a separate, non-randomized stent arm. Patients who met all entry criteria, but were determined by the interventionalist to be too high-risk for stenting, and therefore unable to be randomized, were entered into a separate, non-randomized CEA arm.

Enrollment in the randomized arm of SAPPHIRE was discontinued on June 11, 2002 due to slow enrollment, the unwillingness of surgeons to refer patients, competing non-randomized trials, and waning physician interest in randomizing patients. This did not compromise statistical analysis or interpretation of the trial. The only consequence of early stopping of the trial based on the noted administrative reasons is lower than expected statistical power. Since non-inferiority was still achieved statistically, this consequence was successfully circumvented and the conclusions of the study are not affected. Similarly, the decision to not perform an interim analysis was based on administrative reasons and not on statistical analysis; thus, there is no alpha-penalty to be paid for the final analysis, nor does lack of the interim analysis negate the conclusions made from the final results.

Primary Endpoint: Composite of major adverse events (MAE) including death, any stroke, and/or myocardial infarction at 30-days post-procedure and MAE at 30-days post-procedure plus death and/or ipsilateral stroke between 31 days and 12-months post-procedure.

Number of Patients/Sites: The randomized arm of the SAPPHIRE study enrolled 334 patients (167 stent patients and 167 CEA patients). The non-randomized arms of the SAPPHIRE study enrolled 406 stent patients and 7 CEA patients. Hence, a total of 747 patients were enrolled into SAPPHIRE at 29 centers.

Study Devices: SAPPHIRE investigated the safety and effectiveness of carotid stenting with distal protection utilizing the following Cordis devices:

- Cordis PRECISE™ Nitinol Stent System (5.5F & 6F)
- S.M.A.R.T.™ .018" Nitinol Stent System (earlier version of the 6F PRECISE device)
- ANGIOGUARD™ XP Emboli Capture Guidewire
- ANGIOGUARD™ Emboli Capture Guidewire (earlier version of ANGIOGUARD XP)

Clinical use of the earlier version devices (S.M.A.R.T. .018" and ANGIOGUARD) support the PMA devices in that the device refinements and line extensions were implemented to enhance deliver-ability and reduce profile, which is optimal for carotid artery procedures, and to provide additional sizes to meet the needs of patient anatomies. The changes were minor and unrelated to study endpoints. Delivery system operating principles are the same, SMART Stents have the same finished design, dimensions, and functional requirements as 6F PRECISE Stents, and the ANGIOGUARD and ANGIOGUARD XP basket/filter wire components are identical. Hence, safety of the procedure, effectiveness of the stent, and ability of the filter basket to capture emboli and the force of the basket on the vessel wall are not impacted.

SAPPHIRE utilized the noted over-the-wire (OTW) versions of PRECISE and ANGIOGUARD devices. However, SAPPHIRE clinical results also support rapid-exchange (RX) versions of these devices (Cordis

PRECISE™ RX Nitinol Stent System and ANGIOGUARD™ RX Emboli Capture Guidewire). Device refinements implemented to facilitate rapid-exchange use do not impact primary endpoints of SAPPHIRE. Basic operating principles are the same, the PRECISE stents used in the systems are the same, and the basket/filter wire components of the ANGIOGUARD and ANGIOGUARD XP devices are the same as the ANGIOGUARD RX device. Hence, safety of the procedure, effectiveness of the stent, and ability of the filter basket to capture emboli and the force of the basket on the vessel wall are not impacted. The Food & Drug Administration agreed that bench and animal tests, in conjunction with the results of clinical testing of OTW devices, would be adequate to support RX device safety and effectiveness.

Results:

Randomized Arm: For stent patients, acute clinical results show that lesion success rate was 91.8%, procedure success was 88.1%, device (stent) success was 91.2%, and ANGIOGUARD success was 95.6%. The incidence of MAE at 30 days was 4.8% for stent patients compared to 9.6% for CEA patients. The incidence of MAE at 360 days was 12.0% for stent patients compared to 19.2% for CEA patients.

In comparing treatment arms for MAE at 360 days, the stent arm was non-inferior to the CEA arm within the designated 3% delta (-7.2% [-14.9%, 0.6%]). The difference represented a trend for superiority of the stent arm ($p = 0.067$)

Stent Registry Arm: Acute clinical results showed that the lesion success rate was 90.4%. The procedure success rate was 87.9%. The device (stent) success rate was 89.6%. The ANGIOGUARD success rate was 91.6%. The incidence of MAE at 30 days was 6.9% and at 360 days was 15.8%.

In a test of the primary endpoint against the OPC, despite the fact that the rate was numerically less than the OPC plus the delta, the p value was found to be 0.2899. In a test of the MAE rate when post 30-day non-neurological deaths are not included, the p value was found to be <0.0001. The causes of these non-neurological deaths are well documented, and consist of cardiac deaths, cancer deaths, renal failure, and respiratory failure.

The following clinical reports/information were generated from the SAPPHIRE data.

- SAPPHIRE 1 Year Results – Randomized Arm (Intent to Treat)
  - Appendix I of the SAPPHIRE ITT Report provides a separate analysis of Randomized Evaluable Patients
  - Separate stratification of Randomized SAPPHIRE Patients by Anatomic and Co-morbid Risk Factors is also provided with the SAPPHIRE 1 Year Randomized Arm Report.
- SAPPHIRE – 1 Year Results – Registry Arm
- SAPPHIRE – 1 Year Results – Stent Registry vs. CEA Randomized Results
- Sub-analysis of Non-randomized Stent patients vs. randomized CEA patients
- Preliminary SAPPHIRE 2-Year Results (Randomized ITT Arm)
- Summary of Reasons for Patient Entry in Non-Randomized Stent Arm
- Justification for Treatment of Asymptomatic High Surgical Risk Patients
- Additional Ultrasound Analysis

Conclusion: The results of the pivotal study presented in the SAPPHIRE clinical summaries demonstrate safety and effectiveness of the study devices in treatment of carotid artery disease in patients who are at high risk for surgery.

Feasibility Clinical Study

Background: The Feasibility clinical study began prior to SAPPHIRE under the same IDE. The intent of the study was to confirm device and procedure safety prior to initiation of the SAPPHIRE pivotal study. The study was a multi-center, prospective, open-label feasibility study evaluating the safety and effectiveness of *de novo* or post-endarterectomy restenotic obstructive lesions in native carotid arteries.

Primary Endpoint: 30-day composite of major adverse clinical events including death, any stroke, and/or myocardial infarction.

Number of Patients/Sites: There were 262 patients enrolled into the Feasibility Study at 33 investigational sites. Of those patients, 177 were treated with a stent alone (no distal protection) and 85 patients were treated with stenting and distal protection.

Study Devices: Initially, only stent devices were utilized in this study. An earlier version ANGIOGUARD was introduced later. Ninety ANGIOGUARD devices were used in 85 patients. Study devices consisted of S.M.A.R.T. stent devices, 5.5F PRECISE stent device, and ANGIOGUARD.

Initially, a 7F, 120cm long, .035" guidewire lumen delivery system loaded with S.M.A.R.T. Stents was utilized. The delivery system was modified to taper from 6F proximally to 7F distal, utilize a 135cm working length, and reduce the guidewire lumen to .018". The delivery system was modified once more to include a tapered tip (S.M.A.R.T.™ .018" Nitinol Stent System). Each of these delivery system versions was loaded with the same S.M.A.R.T. Stents.

S.M.A.R.T. devices differed only in the delivery system component. The delivery systems utilized the same operating principle (sheath withdrawal to deploy stent) and consisted of similar materials. The S.M.A.R.T. Stent utilized in the Feasibility Study has the identical design, is comprised of the same material, and has the same finished dimensions as the current 6F PRECISE Stent that was used in the pivotal SAPPHIRE study.

The 5.5F PRECISE device was added to the study. It provided a reduced profile delivery system for delivery of smaller stent diameters (5-8mm). There are only minor dimensional differences between S.M.A.R.T. and 5.5F PRECISE Stents. Basic design, material and performance requirements are the same.

The earlier version ANGIOGUARD device, also utilized in SAPPHIRE, has the same guidewire/basket component as the current ANGIOGUARD XP device. Therefore, the ability to capture emboli and the force of the basket on the vessel wall are the same as ANGIOGUARD XP.

Results: The lesion success rate was 95.8%, procedure success was 90.4%, device (stent) success was 92.3%, and ANGIOGUARD success was 86.7%. The cumulative Major Adverse Event (MAE) rate through 30 days was 6.9% compared with the OPC of 12.7 (p=0.0018). The cumulative MAE rate through 1 year was 10.7%. The following clinical reports were generated from the Feasibility Study data.

- The Cordis Nitinol Carotid Stent and Delivery System (SDS) in Patients with de novo or Restenotic Native Carotid Artery Lesions Trial – Carotid Feasibility Trial – Final Report
  - (includes separate stratification by *de novo* or post-endarterectomy and by investigational center)
- Preliminary Feasibility 2 and 3 Year Results

Conclusion: The results presented in the Feasibility Study clinical summaries help support safety and effectiveness of the devices and procedure in treatment of carotid artery disease.

<u>European Clinical Investigation "CASCADE Study"</u>

Background: The CASCADE Study was sponsored by Cordis and conducted in Europe to help demonstrate safety and performance of the S.M.A.R.T.™ Stent, and later, the ANGIOGUARD™ Emboli Capture Guidewire in carotid artery procedures. The study was a multi-center, prospective, open study.

Primary Endpoint: The primary endpoint was ipsilateral stroke or procedural related death within 30 days of stent implantation. Patients were excluded if they had evidence of medical or surgical risk factors.

Number of Patients: 121 patients with high-grade carotid artery stenosis were entered into this study at 9 investigational sites between September 1998 and May 2001. Ninety (90) patients were treated with the stent device alone. Thirty-one (31) patients were treated with stenting and distal protection.

Study Devices: S.M.A.R.T. Stent* and ANGIOGUARD Emboli Capture Guidewire**
*The S.M.A.R.T. Stent component is identical to the 6F PRECISE Stent component. During the course of the study, earlier version delivery systems were used. The delivery system was enhanced to provide a longer working length (135 vs. 120 cm), a smaller guidewire lumen (.018 vs. .035), a tapered 6/7F profile vs. a 7F profile, and a tapered vs. a non-tapered tip (S.M.A.R.T. .018" Nitinol Stent System).

**The ANGIOGUARD device utilized in this study was an earlier version of the ANGIOGUARD™ XP Emboli Capture Guidewire. The primary component of the device (the basket component) was not changed. Therefore, ability of the device to capture emboli and the force of the basket on the vessel wall are the same as the ANGIOGUARD XP.

Results: Of the 90 patients treated with stenting alone, there were no deaths, 10% had a stroke (2 major) and 8% had a TIA at 30 days. Of the 31 patients treated with stenting and distal protection, there were 0 deaths, no major strokes, 1 minor stroke for an overall event rate of 3.2% at 30 days in these patients. The combined incidence of death, stroke or TIA at 30 days was 14.9% in both patient groups. The following clinical report was generated from the CASCADE study data:

?? The Cordis SMART Self-Expandable Stent in Carotid Artery Disease (CASCADE) Study

Conclusion: The results presented in the CASCADE clinical summary help support safety and effectiveness of the carotid stenting procedure using Cordis devices.

Site-Sponsored IDE Studies

Background: Multiple centers conducted investigator-sponsored studies utilizing Cordis devices. The studies were not sponsored, funded, or monitored by Cordis, nor were the events adjudicated. Each study utilized its own protocol. Hence, patient populations may not be consistent among the various centers and, in most cases, are not consistent with the SAPPHIRE patient population. However, Cordis has made a good faith effort to obtain safety data from the sites in a concise and consistent manner in order to provide an overall summary. To do this, Cordis requested information from the sites to capture baseline demographic, procedural and Cordis device data and subsequent adverse events through 30-days. The data were collected by Harvard Clinical Research Institute (HCRI) and entered into a database for data analysis.

Primary Endpoint: The primary endpoint utilized to assess results of these studies was a composite of major adverse events (MAE) defined as death, any stroke, and/or myocardial infarction at 30 days.

Number of Patients/Sites: A total of 491 patients were enrolled at thirty-four centers.

Study Devices: The Cordis devices utilized were PRECISE Stent devices, S.M.A.R.T. Stent devices, the ANGIOGUARD™ Emboli Capture Guidewire, and the ANGIOGUARD™ XP Emboli Capture Guidewire. In some cases, it is possible that sponsors used Cordis stents with competitor distal protection devices, or competitor stents with the Cordis distal protection devices.

Results: Procedure success at 30 days was 93.8%. Cumulative MAE through 30 days was 4.3%. Detailed results are provided in the clinical summary entitled "The Cordis Nitinol Carotid Stent and Delivery System (SDS) Summary of Individual Site Sponsored Carotid IDE Studies – 30 Day Report" provided in this panel pack.

Conclusion: The results of the site-sponsored studies help support safety and effectiveness of carotid stenting with distal protection using Cordis devices.